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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/357,709	07/20/1999	NEIL H. BANDER	242/026	9637

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EXAMINER
NICKOL, GARY B

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/357,709	BANDER, NEIL H.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68-81,84-95 and 107-132* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68-79, 107-111, 116-132* is/are rejected.

7)☒ Claim(s) *80,81,84-95 and 112-115* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

The Amendment filed October 31, 2002 (Paper No. 22) in response to the Office Action of April 10, 2002 is acknowledged and has been entered.

Claims 82-83, and 96-106 were cancelled.

Claims 108-132 were added.

Claims 68-81, 84-95, and 107-132 are pending and are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

All previous rejections made in Paper No. 19 (mailed 4-10-02) are hereby withdrawn in view of applicant's arguments and in view of the Inventor's declaration submitted under 37 CFR 1.131 in Paper No. 20.

NEW REJECTIONS/OBJECTIONS

Claim Objections

Claims 130-132 are objected to for reciting "e-emiters, E-emitters". These appear to be typographical errors. Further the specification does not define such emitters. See new matter rejection below, too.

Claims 80-81, 84-95, 112-115 are objected to as being dependent from a rejected base claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 78, 108-110, 116-126, 130-132 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth methods encompassing an antibody or antigen binding portion thereof which binds to the extracellular domain of prostate specific membrane antigen (PSMA), or monoclonal antibodies selected from the group consisting of an E99, a J415, a J533, and a J591 (see specification page 24). Thus, the written description is not commensurate in scope with the claims drawn to an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody (Claims 108 and dependents thereof). It is further noted that there is no support in the specification for the specific type of antibody referred to as IgG. Although an IgG antibody is well-known in the art, so are other types of antibodies, such as IgM, IgE, etc, and applicant's have not set forth clearly on the record any support for classifying these particular antibodies as

IgG. Furthermore, there does not appear to be specific support for the radiolabels claimed in Claims 130-132 (i.e., E-emitters, e-emitters) The newly added claims have no clear support in the specification and the claims as originally filed. Hence, this is a new matter rejection. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP § 714.02 and § 2163.06 ("Applicant should specifically point out the support for any amendments made to the disclosure.")

Furthermore, it is noted that applicants argue (Paper No. 20, page 12) that the claimed antibodies are required to compete for binding with a monoclonal antibody selected from the group consisting of E99, J415, J533, and J591. Applicants argue that a skilled artisan "could use" art known methods together with the specific antibodies which have been made publicly available. Applicant's point to Example 10 in the specification that teaches a competition assay. However, example 10 on pages 38-39 is a competition study to determine whether E99, J415, J533, and J591 recognize the same or different antigenic sites- not whether other antibodies could be used to compete for recognition sites of these known antibodies. The results indicated that J591, J533, and E99 all compete for binding to the same antigenic site, whereas J415 recognized a different epitope. The specification only suggests that having pairs of non-competing antibodies (such as J591 and J415) would be useful for detecting "soluble" antigens. For example PSMA could be captured by J591 and detected by J415. Hence, the results do not provide evidence of or a written description for other antibodies (or antigen binding portions

thereof) which compete for binding to PSMA with a monoclonal antibody selected from the group consisting of E99, J415, J533, and J591.

Claim Rejections - 35 USC § 102

The rejection under 35 USC 102(e) and being anticipated by Israeli *et al.* (US Patent No. 5,538,866) in Paper No. 6, page 7 is hereby re-instated. Modification to this rejection appear below.

This rejection corresponds to claims 68-70, 76-77, 79, 111, 116-117, 119-121, 126-128. (It is noted in the prior office action of Paper No. 6, page 8, the previous examiner recited that Israeli *et al.* does not specifically teach "detection after prostatectomy". However, Israeli does teach detection after prostatectomy; see column 22, line 47.)

Although Israeli *et al.* do not specifically teach that the antibodies of the invention bind specifically to live cells (i.e. see Claim 111), inherently such antibodies as taught by Israeli *et al.* would bind to living or dead cells or to wherever type of cell comprises PSMA as antibodies do not discriminate between cell types- only those cell types that comprise the specific antigen binding sites recognized by an antibody directed to PSMA. Furthermore, the previous action stated (page 7) that "Although Israeli does not explicitly state that the antibody or ligand binds to the extracellular domain of PSMA [sic], Israeli teaches in general antibodies which bind to PSMA, and includes extensive structural information including the entire nucleic acid sequence of the antigen and the guidance necessary to create antibodies to any portion of the antigen." Israeli also teaches (column 6, lines 48+; column 12, lines 64+) polyclonal and monoclonal antibodies directed to **specific portions** of the PSMA antigen. Absent evidence to the contrary,

these portions also appear to be portions of the extracellular domain since the present specification does not specifically teach which regions of PSMA constitute the extracellular domain. Furthermore, although "extracellular domain" is not specifically mentioned, the patent teaches that one of ordinary skill could select "specific regions" on PSMA to generate antibodies (column 12, lines 32+). This includes hydrophilic regions located on the "cell surface". To those of ordinary skill in the art, the cell surface is outside the cytoplasm and would comprise extracellular epitopes of PSMA. The patent further teaches, under antigenic site identification, (column 22), that the knowledge of the cDNA for the antigen also provides for the identification of areas that would serve as good antigens for the development of antibodies for use against specific amino acid sequences of the antigen. Such sequences may be at different regions of the antigen such as "outside", membrane or inside of the PSM antigen. The patent further teaches (column 22, lines 40+), that the cDNA sequence implies that the antigen has the characteristics of a membrane spanning protein, with the majority of the protein on the exofacial surface. Thus, since it is clear that PSMA is a "membrane spanning protein", and since such proteins encompass intracellular, membrane spanning, and extracellular antigenic sites, the reference clearly anticipates antibodies to all regions or portions of the antigen- including those to the extracellular domain(s).

The Bander Declaration along with the accompanying arguments (Paper No. 8, pages 16-19 have been reconsidered and are not found persuasive to overcome the above rejection under Israeli *et al.* First, the Bander Declaration (Bander Declaration #1, Item 17, page 7) does not address the teachings of the Israeli patent, but instead addresses an article by Israeli in Cancer Research. Thus, such arguments will not be considered because the article in Cancer Research

was not used to support the 102 rejection above. Secondly, applicants' arguments which incorporated the Bander Declaration and the teachings of the Israeli patent (Paper No. 8, pages 16-19) were reconsidered and are also not found persuasive. Applicants generally argue against the operability of using synthetic amino acid sequences of PSMA as an immunogens to develop antibodies (pages 16-17) whereas the method of the presently filed application chooses to use viable-unmodified prostate cancer cells. Applicants argue that their methodology is superior because the native PSMA glycoprotein is presented to the immunized animals' immune system in a form whereby generated antibodies recognize the native glycoprotein as it exists on an integral membrane protein of a living cell. This argument has been considered but is not found persuasive because such arguments rely on particular distinguishing features (i.e. they are limited to monoclonal antibodies; see specification page 17, lines 5+) and are not persuasive when those features are not recited in the claims. Narrow limitation contained in the specification cannot be inferred in the claims where the elements not set forth in the claims are linchpin of patentability. See In re Philips Industries, Inc. v. State Stove & Mfg. Co., 522 F.2d 1137, 186 USPQ 458 (CA6 1975), 237 PTJA A-12. While the claims are to be interpreted in light of the specification, it does not follow that limitations from the specification may be read into claims. On the contrary, claims must be interpreted as broadly as their terms reasonably allow. See Ex parte Oetiker, 23 USPQ2d 1641 (BPAI, 1992). Moreover, with regards to the operability/enablement of the Israeli patent, a patent shall be presumed **valid** for all that it teaches which includes the presumption of operability (MPEP 716.07). Thus, the fact that applicant's argue "that one cannot be certain how well exposed such a peptide is nor how immunogenic it is" does not constitute a preponderance of evidence against the enablement and use of antibodies to the extracellular domain of PSMA.

Further, it is to be presumed that skilled workers would as a matter of course, if they do not immediately obtain desired results, make certain experiments and adaptations, within the skill of the competent worker. Furthermore, as set forth above, Israeli *et al.* teaches that one of ordinary skill could select "specific regions" on PSMA to generate antibodies (column 12, lines 32+), wherein the patent clearly set forth the characteristics of PSMA as being a membrane spanning protein which includes hydrophilic regions located on the cell surface. Thus, applicant's arguments (Paper No. 8, page 17) which allege that the Israeli patent does not teach *which part* of the protein should be used produce antibodies which will reliably detect the presence of PSMA as an integral membrane protein on the surface of a living cell is also not found persuasive, particularly when the present specification also does not teach which part of the protein should be used to produce antibodies against the extracellular domain.

Arguments addressing the 7E11 monoclonal antibody to PSMA (pages 17-18) as being an example of how difficult it may be to make a monoclonal antibody to the extracellular domain of PSMA have been considered but are also not found persuasive. The arguments are irrelevant because they have merely set forth the confusion surrounding the location of the epitope recognized by 7E11. In other words, epitope mapping of a *known* monoclonal antibody does not unequivocally suggest to a skilled worker how difficult it may be to **make** a monoclonal antibody to the extracellular domain of PSMA. In fact, Israeli *et al.* appreciated the prior success of the 7E11 antibody (column 2, lines 35+) which would suggest to the skilled worker that other antibodies specific for PSMA would bind to PSMA, regardless of their specificity for extracellular or intracellular domains. Also, applicants' argue that they are unaware of any antibodies that have been made using a synthetic sequence of PSMA that will bind to viable

prostate cancer cells. This argument has been considered but is not found persuasive. The fact that applicant's are simply "unaware" of the production of such antibodies does not cast reasonable doubt that other skilled workers in the field of immunology or cancer diagnosis could not produce antibodies to the extracellular domain of PSMA. The subject matter and quoting of Troyer *et al.* has also been considered but is not found relevant because the central thrust of Troyer *et al.* was to determine how the 7E11 antibody could image occult prostate carcinomas if it could not penetrate the plasma membrane of intact cancer cells (see Troyer *et al.* , page 239, 1st column, discussion); not how difficult it was to make monoclonal antibodies to the extracellular domain of PSMA or how difficult it was to make antibodies against synthetic amino acids of PSMA. In fact, the teachings of Troyer *et al.* suggest that one **should** develop antibodies against the extracellular domain of PSMA because such antibodies may dramatically increase the sensitivities of imaging assays (Troyer *et al.*, page 240, 2nd column, last paragraph, and page 241, last paragraph). Thus, applicant's arguments that "the prior art's experience with antibodies to PSMA demonstrates that obtaining an antibody with binds to the external domain is hardly a matter of routing experimentation" is not found persuasive. It is further maintained that although Israeli *et al.* is somewhat silent as to the internalization of the antibody, such phenomenon are well known to occur. Applicants have argued that the Coleman *et al.* reference is non-analogous since the reference of Coleman *et al.* demonstrated such activity in hematological cells versus epithelial cells, such as prostate cancer. This argument has been considered but is not found persuasive. Such an argument does not unequivocally demonstrate that antibodies against the extracellular domain of PSMA would not be internalized in epithelial cells. The argument is that they would inherently do so based on such art-recognized phenomenon. Furthermore, Israeli *et*

al. does recognize that tumor cells tend to express increased levels of transferrin receptor (a cell surface antigen). Since transferrin receptor antibodies with toxin conjugates are cytotoxic to these tumor cells via "endocytosis", Israeli *et al.* suggest that antibodies against PSM coupled with a cytotoxic agent would be useful in a clinical setting since they would be internalized like the transferring receptor (column 23, lines 35+). Thus, applicant's arguments have not been found persuasive.

Claim Rejections - 35 USC § 103

Claims 68-70, 76-77, 79, 111, 116-117, 119-121, 126-128, as set forth above, and Claims **71-75, 78, 118, 122-125, 129** are rejected under 35 U.S.C. 103(a) as being unpatentable over Israeli *et al.* (US Patent No. 5,538,866, 1994) in view of the teachings of Thomas *et al.* (Antibodies, A practical approach, Vol. 2, 1988) or Schlom, in "Molecular Foundations of Oncology", Chapter 6, pages 93-134, IDS)

Israeli *et al.* teach as set forth above.

Israeli *et al.* fail to teach specific modes of administration such as parenteral (Claim 71), intravenous (Claim 72), intracavitary instillation (Claim 73), and rectal (Claim 74). Israeli *et al.* fail to teach wherein the label is detected using a transrectal probe (Claim 75). Israeli fail to specifically teach that the antibody is an IgG (Claims 78 and 129) or that the antibody or antigen binding portions thereof can be Fab fragments, $F(ab')_2$ fragments, or Fv fragments (Claim 118). Israel *et al.* also fail to include specific types of radiolabels (except ^{111}In- see column 13, line 18) such as ^{212}Bi, ^{213}Bi, and ^{211}At (Claim 122) or ^{32}P, ^{125}I, ^{3}H, ^{14}C, and ^{188}Rh (Claim 123), or ^{131}I (Claim 124), or ^{99}mTc (Claim 125).

The specific imagining techniques, modes of administration, antibody fragments are well known in the art as set forth in applicant's disclosure of admitted prior art (pages 21-25). Also, Thomas *et al.* teach that antibodies can be used for in-vivo imaging, including an imaging device, antibody internalization, and radiation emitters including ^{131}I, ^{99}mTc, or ^{111}I. Thomas *et al.* further teach that radiolabeled sheep and goat IgG antibodies have been used predominately (page 226, and 230). Also, Schlom teaches that antibodies can be used for in vivo imaging, including an imaging device (i.e., probes, page 103), intravenous and intracavity administration (i.e, page 101), antibody internalization, and radiation emitters including short range eitters, ^{125}I, ^{131}I, ^{99}mTc, or ^{111}I. Schlom also teaches that antibody fragments such as Fab fragments are well known in the art (page 97).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the assays taught in Israeli *et al.* (US Patent No. 5,538,866) so as to include the specific imagining techniques, modes of administration, antibody fragments, as well as the antibody IgG, and one would have been motivated to do so because these techniques are well-known in the art, include art-recognized equivalents and variations, wherein one of ordinary skill in the art would have a reasonable expectation of success in implementing the modifications for the purposes associated with diagnostic applications.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
January 13, 2003

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